# Serum Sex-hormone-binding Globulin is Related to Hepatic and Peripheral Insulin Sensitivity But Not to Beta-cell Function in Men and Women With Type 2 Diabetes Mellitus

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**This study examined the relationship of hepatic and peripheral insulin sensitivity and $\beta$-cell secretory function with serum sex hormone-binding globulin (SHBG) in men and women with Type 2 diabetes mellitus (DM). Fasting insulin, glucose and SHBG were measured in 58 Type 2 diabetic patients of both sexes (36 men) who were on diet treatment only and terms for insulin sensitivity and $\beta$-cell secretion obtained by modelling. There was no significant difference in SHBG between men and women despite similar degree of obesity. SHBG was positively correlated ($r = 0.41$, $p < 0.01$) to hepatic insulin sensitivity derived from mathematical modelling of fasting glucose and insulin data using the homeostasis assessment model (HOMA). This relationship was independent of gender (men, $r = 0.48$, $p < 0.01$; women, $r = 0.45$, $p < 0.05$). Fasting insulin correlated negatively with SHBG in men ($r = -0.34$, $p < 0.05$). There were also significant negative correlations between SHBG and either plasma glucose ($r = -0.29$, $p < 0.05$) or body mass index ($r = -0.34$, $p < 0.05$). SHBG did not correlate with HOMA-modelled beta-cell function. In a multiple regression analysis, SHBG was independently correlated only with insulin sensitivity ($p < 0.05$). Further studies in 15 of the diabetic patients (11 men), showed a significant positive correlation ($r = 0.52$, $p < 0.05$) between SHBG and peripheral insulin sensitivity derived by continuous infusion of glucose with model assessment (CIGMA) but not between SHBG and CIGMA-modelled $\beta$-cell function. These results indicate that both hepatic and peripheral insulin sensitivity are similarly related to serum SHBG in Type 2 diabetes of both sexes. The sex-difference in SHBG was abolished in the patients.** **© 1998 John Wiley & Sons, Ltd.**

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## Introduction

Sex-hormone-binding globulin (SHBG) is secreted and catabolized by the liver,[1] which is also a major site of insulin action and glucoregulation. Previous studies have suggested a link between SHBG and insulin sensitivity and/or secretion in man. For example, in a study of women with polycystic ovary syndrome (PCOS) a negative correlation was found between serum SHBG and fasting insulin levels,[2] while in normal healthy pre-menopausal women, SHBG was found to be negatively related to an insulin response to a glucose load in a manner independent of fat mass.[3] These observations have since been confirmed in a large epidemiological study of pre-menopausal and post-menopausal women.[4] Further *in vitro* studies have shown that insulin reduces SHBG secretion directly and also inhibits the stimulatory action of thyroxine and oestradiol on its synthesis in the human hepatoma cell line Hep G2.[5,6] It has also been demonstrated that manipulations which decrease insulin secretion such as the administration of a very low calorie diet or treatment with diazoxide cause an increase in serum SHBG in patients with PCOS and in normal women.[7–9] These results are consistent with a decrease in SHBG secretion *in vivo* as a major consequence of the hepatic action of insulin, although catabolic effects on SHBG degradation cannot be ruled out. In men with

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Type 2 diabetes, SHBG has been shown to be positively correlated to whole body insulin sensitivity but not circulating C-peptide or insulin, in a manner independent of adiposity or fat distribution.[10] This observation has been confirmed in normal men but was absent in men with Type 1 diabetes in whom circulating SHBG correlated negatively with insulin dose.[11] Further studies in non-diabetic men have shown that SHBG is negatively correlated to insulin secretory pulse frequency.[12] There is evidence from two prospective studies that SHBG is a predictor for development of Type 2 diabetes in women and not in men.[13,14]

There are few published data on the relationship between SHBG and insulin sensitivity in women with Type 2 diabetes. We also are not aware to date of any reports examining formally how SHBG is related to β-cell secretory function in either sex. Previous studies have concentrated mostly on the relationship between peripheral insulin sensitivity and SHBG and there is no information on the influence of central or hepatic insulin sensitivity. This study set out to examine these issues in patients of both sexes with Type 2 diabetes mellitus.

## Patients and Methods

### Subjects

Fifty-eight patients with Type 2 diabetes (36 men and 22 women) were studied after obtaining informed consent. The subjects had been on diet treatment only (approximately 50% of calories derived from carbohydrate with a low saturated fat and high fibre content) for control of their diabetes for between 1 week and 9 months. None of the patients was on any medication likely to interfere with SHBG metabolism including androgens, oestrogens, progestogens, thyroid hormones or glucocorticoids. The characteristics of the patients are shown in Table 1. This study had the approval of the Ethics Committee of the Central Manchester Healthcare Trust according to the declaration of Helsinki.

### Experimental Procedures

Blood samples were obtained from all patients at a routine clinic visit after an overnight fast. Plasma was obtained for measurement of glucose and insulin and serum for testosterone, thyroxine (T4), triiodothyronine (T3), and SHBG. Glycosylated haemoglobin was measured in whole blood. Insulin sensitivity and $\beta$-cell function were derived by mathematical modelling from paired fasting plasma glucose and insulin values by the technique of homeostasis model assessment (HOMA).[15] Fifteen of the patients were also studied by continuous infusion of glucose with model assessment (CIGMA). A 60 -min constant infusion of low-dose glucose (5 mg $kg^{-1}$ ideal body weight) was given intravenously. Venous blood samples were taken at −10, −5, and 0 min before infusion and at 50, 55, and 60 min during the infusion, after a steady state had been reached. Glucose, insulin, and C-peptide were measured on all samples taken during the test and SHBG on the sample taken at 0 min only. For each subject, the fasting values of each analyte were calculated as the mean of the three basal values and the 'achieved' values derived as mean of the 50, 55, and 60 min values. Insulin sensitivity and $\beta$-cell function were derived from the 'achieved' plasma and glucose concentrations according to the CIGMA model.[16]

### Analytical methods

Sex hormone binding globulin was measured by a two-site immunoradiometric assay kit (Orion, Finland) with within and between batch coefficients of variation (CV) of 5 % and 7 %, respectively, at 20 nmol $l^{-1}$. Insulin was measured by a competitive radioimmunoassay using dextran-coated charcoal separation. Polyclonal guinea pig anti-human insulin serum was obtained from ICN Biomedical (Costa Mesa, California, USA) and $^{125}I$ labelled human insulin, purified by high pressure liquid chromatography, was obtained from Medgenix SA, Fleurys, Belgium. The within and between batch CV of the insulin assay were 5 % and 8 %, respectively, at 100 pmol $l^{-1}$ and the cross-reactivity of proinsulin with the antiserum was 35 %. Human insulin used as assay standard (1st International Reference Preparation 66/304) and human proinsulin (International Reference Reagent 84/611) for cross-reactivity studies were obtained from the National Institute for Biological Standards and Control, South Mimms, Hertfordshire, UK. Cross-reactivity was assessed by assay of a range of proinsulin standards which gave complete displacement of the insulin tracer and a parallel dose–response curve to the insulin standards. C-peptide was measured using a commercial radioimmunoassay kit supplied by Medgenix with a within and between batch CV of less than 5.5 % in the analyte range 0.1–5.0 nmol $l^{-1}$. Glucose was measured using a glucose-oxidase method and haemoglobin $A_1$ ($HbA_1$) by electrophoresis and densitometry using the Corning Glycotrac apparatus with a CV of 3.5 %. Testosterone was measured using a direct coated tube radioimmunoassay with 125I label (Euro/DPC Ltd, Llanberis, Gwynned, UK). T3 and T4 were measured in serum by double antibody radioimmunoassay using in-house reagents; within and between batch CV were less than 5 % and 10 %, respectively.

### Assessment of Insulin Sensitivity and $\beta$-Cell Function

Insulin sensitivity and $\beta$-cell function were derived from glucose and insulin data by the HOMA[15] and CIGMA[16] mathematical models. HOMA-derived insulin sensitivity is thought to correlate primarily with hepatic insulin sensitivity whereas that derived by the CIGMA method reflects primarily peripheral insulin sensitivity. These models assume that the control of plasma glucose and



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Table 1. Clinical and biochemical characteristics of the 58 patients with Type 2 diabetes

| | All patients | Men | Women |
|---|---|---|---|
| Number of patients | 58 | 36 | 22 |
| Age (yr) | 55 (45–58) | 55 (45–57) | 55 (48–60) |
| Body mass index (kg $m^{-2}$) | 28.7 (26–34) | 28 (27–34) | 29 (26–33) |
| $HbA_1$(%) | 10 (7.8–11.8) | 9.7 (7.3–11.9) | 10.4 (8.9–12.0) |
| Fasting plasma glucose (mmol $l^{-1}$) | 8.5 (7.1–11.2) | 7.9 (6.7–10.1) | 9.5 (8.0–11.9) |
| Fasting plasma insulin (pmol $l^{-1}$) | 70 (40–117) | 73 (31–152) | 65 (53–94) |
| Sex-hormone-binding globulin (nmol $l^{-1}$) | 22.1 (16–28) | 20.6 (15–32) | 22.7 (17–26) |
| Testosterone (nmol $l^{-1}$) | 8.9 (1.1–16.9) | 16.2 (12.4–18.5)[a] | 1.1 (1.0–1.4) |
| Thyroxine (T4) (nmol $l^{-1}$) | 97 ± 20 | 98 ± 18 | 98 ± 18 |
| Triiodothyronine (T3) (nmol $l^{-1}$) | 1.69 ± 0.36 | 1.73 ± 0.41 | 1.65 ± 0.27 |
| HOMA-insulin sensitivity | 0.24 (0.12–0.37) | 0.25 (0.12–0.43) | 0.19 (0.12–0.30) |
| HOMA-$\beta$-cell function (%) | 43.7 (24.4–90.4) | 47.1 (27.0–98.3) | 38.0 (21.7–59.5) |

Data are median (interquartile range) except T4 and T3 (mean ± SD).
HOMA, homeostasis model assessment.
[a] $p < 0.0001$, compared with women.

insulin in the fasted state (HOMA) and after a continuous low dose infusion of glucose (CIGMA) are determined by a negative feedback loop involving the pancreatic $\beta$-cells, liver, insulin-sensitive and insulin-insensitive tissues. Beta-cell function and insulin sensitivity for each subject are expressed as a proportion of those for a reference population with notional values of 100 % and 1, respectively. For the HOMA procedure, insulin sensitivity was derived from the formula:

$$\text{HOMA-S} = 146/(\text{insulin} \times \text{glucose}).$$

Beta-cell function is given by:

$$\text{HOMA-}\beta = 3.08 \times \text{insulin}/(\text{glucose-}3.5).$$

These formulae were modified from the original publication[15] to take into account our use of pmol $l^{-1}$ for insulin concentrations rather than mU $l^{-1}$, assuming 1mU insulin = 6.5 pmol. The CIGMA indices of insulin sensitivity and $\beta$-cell function were derived from an expanded version of the published normogram[16] obtained from J. Hosker, Department of Medicine, Doncaster Royal Infirmary, Doncaster, UK.

### *Statistical Analysis*

Statistical analysis was performed using the Minitab package (Minitab Inc., State College, Pennsylvania, USA). The significance of the difference between medians was assessed by the Mann-Whitney U-test and the paired Wilcoxon test. The Spearman rank correlation coefficient was used as a test of association. For multiple regression analysis, data were log-transformed as necessary. Significance was accepted at $2p < 0.05$.

## Results

The clinical and biochemical characteristics of the 58 patients are given in Table 1. There were no sex differences in all indices of glucose and insulin metabolism. Furthermore, SHBG concentrations were similar between men and women despite similar degree of obesity and marked differences in testosterone levels.

A summary of univariate correlation between SHBG and the various parameters studied is given in Table 2. A significant positive correlation was obtained between SHBG and HOMA-insulin sensitivity ($r = 0.41$, $p < 0.01$; Figure 1) and the relationship was independent of gender (men, $r = 0.48$, $p < 0.01$; women $r = 0.45$, $p < 0.05$). SHBG was also significantly related to body mass index in the patient group as a whole ($r = -0.34$, $p < 0.05$) and in men ($r = -0.39$, $p < 0.05$) but not in women. Fasting plasma glucose was correlated with SHBG in the whole patient group ($r = -0.29$, $p < 0.05$) and in women ($r = -0.48$, $p < 0.05$) but not in men. Fasting plasma insulin was negatively correlated to SHBG in men only ($r = -0.34$, $p < 0.05$). There was a significant



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Table 2. Univariate correlation of sex-hormone-binding globulin with other parameters in 58 patients with Type 2 diabetes

| | All patients | Men | Women |
|---|---|---|---|
| Body mass index (kg m$^{-2}$) | $-0.34^{a}$ | $-0.39^{a}$ | $-0.35$ |
| $HbA_1$ (%) | $-0.22$ | $-0.31$ | $-0.02$ |
| Fasting plasma glucose (mmol l$^{-1}$) | $-0.29^{a}$ | $-0.26$ | $-0.48^{a}$ |
| Fasting plasma insulin (pmol l$^{-1}$) | $-0.24$ | $-0.34^{a}$ | $-0.11$ |
| HOMA-insulin sensitivity | $0.41^{b}$ | $0.48^{b}$ | $0.45^{a}$ |
| HOMA-$\beta$-cell function (%) | $-0.14$ | $-0.22$ | $-0.15$ |
| Testosterone (nmol l$^{-1}$) | 0.15 | $0.60^{b}$ | 0.004 |
| Thyroxine (nmol l$^{-1}$) | 0.10 | 0.07 | 0.15 |
| Triiodothyronine (nmol l$^{-1}$) | 0.02 | 0.09 | $-0.10$ |

Values are Spearman's correlation coefficient.
HOMA, homeostasis model assessment.
$^{a}p < 0.05$, $^{b}p < 0.01$.

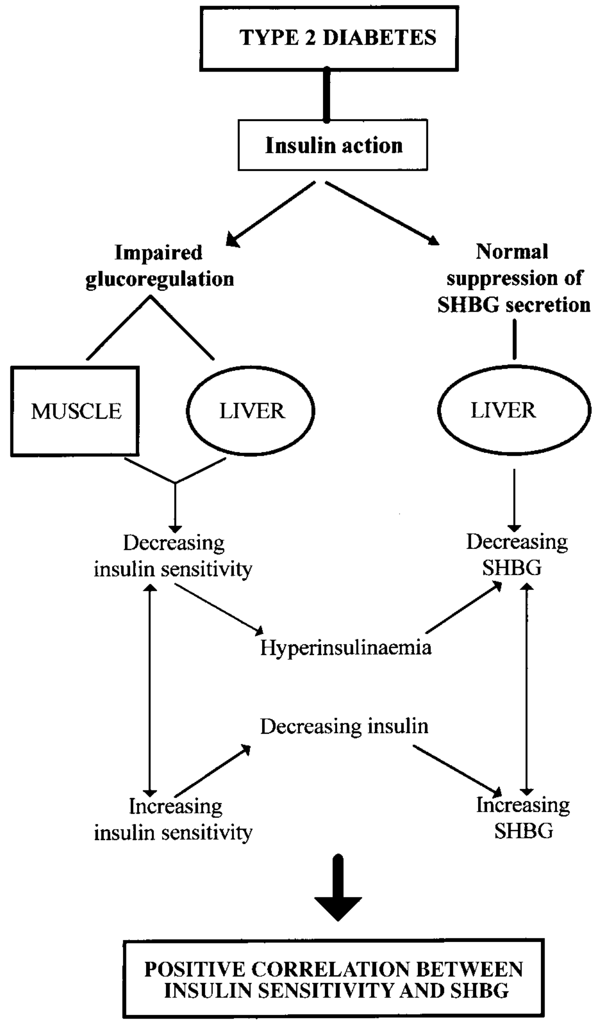


Figure 2. Proposed scheme for selective insulin action with respect to glucoregulation and regulation of sex hormone binding globulin (SHBG) in Type 2 diabetes

positive relationship between SHBG and testosterone ($r = 0.60$, $p < 0.01$) in men but not in women. SHBG was not significantly correlated with HOMA-$\beta$-cell function, $HbA_1$, T3, and T4. In a multiple regression analysis, SHBG was only independently related to HOMA-insulin sensitivity ($p < 0.05$).

The data on CIGMA studies in 15 of the diabetic patients are shown in Table 3. SHBG was positively correlated with CIGMA-insulin sensitivity ($r = 0.52$, $p < 0.05$). There was no significant relationship between SHBG and CIGMA-$\beta$-cell function.

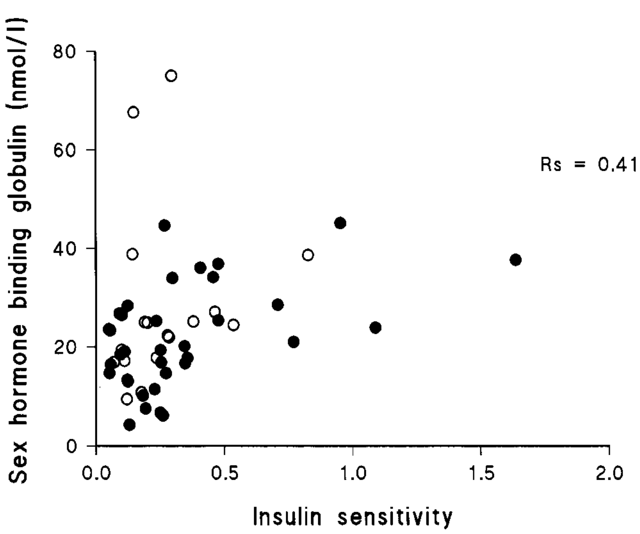


Figure 1. The relationship between insulin sensitivity and sex hormone binding globulin (SHBG) in 36 men (●) and 22 women (○) with Type 2 diabetes. Rs is Spearman's correlation coefficient

## Discussion

The results reported here further emphasize the relationship between insulin sensitivity and circulating SHBG. The relationship was observed in both sexes and, for the first time, in women with Type 2 diabetes. Its independence from body mass and indices of glycaemic control has been reported previously.[3,8–10] Furthermore, using two different techniques based on the same modelling principles to assess insulin sensitivity, we have shown that SHBG is positively related to both the peripheral and hepatic glucoregulatory actions of insulin. The HOMA technique is considered to reflect hepatic rather than peripheral insulin sensitivity[15] while the CIGMA is thought to assess principally peripheral insulin sensitivity.[16] Evidence from *in vitro*[5,6] and *in vivo*[7–9] studies



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Table 3. Clinical and biochemical parameters in 15 Type 2 diabetic patients studied by the CIGMA technique

| | Median (interquartile range) |
|---|---|
| Male/female | 11/4 |
| Age (yr) | 51 (42–58) |
| BMI (kg $m^{-2}$) | 27 (25–32) |
| $HbA_1$ (%) | 10.4 (8.5–13.8) |
| Sex-hormone-binding globulin (nmol $l^{-1}$) | 19 (14–28) |
| Plasma glucose (mmol $l^{-1}$) | |
| fasting | 9.6 (8.1–11.6) |
| achieved | 14.0 (11.2–15.1) |
| Plasma insulin (pmol $l^{-1}$) | |
| fasting | 60 (53–108) |
| achieved | 90 (55–145) |
| Plasma C-peptide (nmol $l^{-1}$) | |
| fasting | 0.58 (0.43–0.76) |
| achieved | 0.72 (0.49–0.87) |
| CIGMA-insulin sensitivity | 0.31 (0.24–0.56) |
| CIGMA-$\beta$-cell function (%) | 25 (18–45) |

CIGMA, continuous infusion of glucose with model assessment.

indicate that the action of insulin is to downregulate SHBG secretion. This then raises the question of how the positive association between SHBG and insulin sensitivity which we and others have observed occurs. We propose that this can be explained only if the actions of insulin with respect to glucoregulation and to modulation of SHBG processing by the liver were to be largely independent and selective; such that in our diabetic patients, the suppressive action of insulin on SHBG secretion by the hepatocyte is intact and appropriate in the face of central and peripheral impairment of its glucoregulatory action. If this is true, the situation then arises whereby impaired sensitivity to insulin-mediated glucoregulation results in hyperinsulinaemia which will enhance suppression of SHBG secretion. Conversely, as insulin sensitivity improves, insulin concentrations fall with consequent improvement in SHBG secretion (Figure 2). This hypothesis is consistent with the increases in serum SHBG concentrations observed with manoeuvres such as weight loss which enhance insulin sensitivity.

Selective sensitivity to other *in vivo* actions of insulin is not a novel concept. It has already been described for the suppression of non-esterified fatty acids[17,18] and modulation of trans-cellular potassium flux.[17,19,20] Indeed, in normally insulin sensitive individuals, the sensitivity of peripheral tissues to insulin-mediated glucose disposal is much less than that of the sensitivity of the liver to suppressive action of insulin on glucose production.[21] It has been suggested that serum SHBG may be a marker of insulin sensitivity.[22] However, we would argue that SHBG may mirror insulin sensitivity only in the presence of hyperinsulinaemia in individuals with intact insulin secretion.[9,11] This perhaps explains why SHBG is unrelated to peripheral insulin sensitivity in patients with Type 1 diabetes.[11] Furthermore, it highlights the likely importance of hyperinsulinaemia in the regulation of SHBG.

The absence of a sex-difference in SHBG concentrations observed in this study, despite diabetic men and women both having similar degrees of obesity and insulin sensitivity, is noteworthy. This serendipitous observation is in contrast to the higher SHBG seen in non-diabetic women compared to non-diabetic men.[1] Lack of a sex-difference in SHBG has been previously noted in a longitudinal study of men and women who later developed Type 2 diabetes, who had similar body mass indices;[14] the women also had lower SHBG levels than age-matched control female subjects. Our diabetic women, though obese, had no clinical or biochemical features of the polycystic ovarian syndrome (although ovarian ultrasound was not performed) which is usually associated with low SHBG levels, so this is unlikely to have been a confounding factor. The physiological and clinical implication of diabetic women having equivalent concentrations of SHBG to those of men is not clear. However, in this context, it is interesting to note that low SHBG has been implicated as a predictor for development of Type 2 diabetes in women but not in men in two prospective studies.[13,14]

Factors other than insulin affect circulating SHBG. Under physiological circumstances androgens, oestrogens, thyroid hormones, glucocorticoids growth hormone, and insulin-like growth factor (IGF-1) are potential modulators; some perhaps through insulin-mediated mechanisms.[1,11] While it is difficult to exclude confounding influences of these other factors in the present study, our patients were clinically and biochemically euthyroid; had testosterone levels appropriate to their sexes; the women did did not have clinical evidence of androgenization; and none of the patients was on any medication likely to affect SHBG. The fact that no sex difference in SHBG was observed despite considerable differences in circulating testosterone between the men and women suggests that insulin sensitivity may be the more important modulating factor. This observation may also suggest a possible difference in the androgen modulation of SHBG between the sexes.

Insulin action can be regarded as a composite of insulin sensitivity and $\beta$-cell function. While insulin sensitivity was clearly related to SHBG, we found no relationship between the protein and $\beta$-cell secretory function derived using either of the models studied. This observation is similar to those made by Birkeland *et al.* who found no association between SHBG and basal concentrations of C-peptide, a surrogate marker of $\beta$-cell function, despite a strong relationship between the former and insulin sensitivity in men with Type 2 diabetes.[10] However, in one study of non-diabetic subjects, basal concentrations of C-peptide correlated



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significantly with SHBG;[11] and in another study of normal men, insulin secretory pulses but not the estimated insulin secretory rates were related to SHBG.[12] It does appear, therefore, that both quantitative and qualitative aspects of insulin secretion are important for regulation of SHBG; these intricate processes may be differentially controlled in the diabetic and non-diabetic states. The situation is equally complex with regards to the relationship of SHBG with fasting insulin concentrations. In contrast to patients with essentially normal glucose tolerance in whom a clear cut relationship of SHBG with fasting insulin has been shown,[2,3,6] this relationship was discernible only in our male diabetic patients but not the female. In keeping with our finding, this relationship was also demonstrated in one study of men with Type 2 diabetes,[9] but much less so in another similar study.[10] However, it has been acknowledged that while fasting insulin is closely related to other indices of insulin action in euglycaemic individuals, the relationship is less clear cut in Type 2 diabetes.[13,14]

In conclusion, we have shown that serum SHBG is positively related to both hepatic and peripheral insulin sensitivity not only in men with Type 2 diabetes but also in women. An argument has been made for interpreting this relationship as being consistent with selectivity and divergence in the actions of insulin in terms of glucoregulation and regulation of SHBG economy. Furthermore, the well-known sex-difference in SHBG levels in non-diabetic individuals appears to be abolished in Type 2 diabetes. The implications of female diabetic patients having serum SHBG concentrations in the range more normally seen in men require further study.

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